Levetiracetam Versus Phenobarbital for Neonatal Seizures: A Randomized Controlled Trial

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abstract

BACKGROUND AND OBJECTIVES: There are no US Food and Drug Administration–approved therapies for neonatal seizures. Phenobarbital and phenytoin frequently fail to control seizures. There are concerns about the safety of seizure medications in the developing brain. Levetiracetam has proven efficacy and an excellent safety profile in older patients; therefore, there is great interest in its use in neonates. However, randomized studies have not been performed. Our objectives were to study the efficacy and safety of levetiracetam compared with phenobarbital as a first-line treatment of neonatal seizures.

METHODS: The study was a multicenter, randomized, blinded, controlled, phase IIb trial investigating the efficacy and safety of levetiracetam compared with phenobarbital as a first-line treatment for neonatal seizures of any cause. The primary outcome measure was complete seizure freedom for 24 hours, assessed by independent review of the EEGs by 2 neurophysiologists.

RESULTS: Eighty percent of patients (24 of 30) randomly assigned to phenobarbital remained seizure free for 24 hours, compared with 28% of patients (15 of 53) randomly assigned to levetiracetam ($P < .001$; relative risk 0.35 [95% confidence interval: 0.22–0.56]; modified intention-to-treat population). A 7.5% improvement in efficacy was achieved with a dose escalation of levetiracetam from 40 to 60 mg/kg. More adverse effects were seen in subjects randomly assigned to phenobarbital (not statistically significant).

CONCLUSIONS: In this phase IIb study, phenobarbital was more effective than levetiracetam for the treatment of neonatal seizures. Higher rates of adverse effects were seen with phenobarbital treatment. Higher-dose studies of levetiracetam are warranted, and definitive studies with long-term outcome measures are needed.

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WHAT'S KNOWN ON THIS SUBJECT: In 1999, a randomized controlled trial comparing phenobarbital and phenytoin in neonates revealed that each drug had 45% efficacy. These treatments remain the standard of care for neonatal seizures. Levetiracetam has a better safety profile; however, its efficacy is unproven in neonates.

WHAT THIS STUDY ADDS: In this study conducted in the hypothermia era and with near real-time response to continuous video EEG monitoring, phenobarbital was more effective than levetiracetam in achieving seizure cessation. Dose-finding studies and phase III trials with long-term outcomes are needed.

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Neonatal seizures affect 1 to 4 of 1000 newborns[1] and are associated with poor outcomes: 7% to 33% of infants with neonatal seizures die, and 40% to 60% of survivors have permanent disabilities, including cerebral palsy, global developmental delay, and epilepsy.[2] Mortality and morbidity of neonatal seizures are in large part attributed to the underlying condition; however, there is mounting evidence that seizures themselves are harmful, especially in the asphyxiated neonatal brain.[3–9] Neonatal seizures frequently fail to respond to the most common treatments: phenobarbital and phenytoin.[10–13] Acute side effects of phenobarbital include hypotension, respiratory suppression, and sedation; chronic exposure to phenobarbital may cause decreased cognitive ability.[14–17] In animal studies, phenobarbital causes accelerated neuronal apoptosis in the immature brain.[18–22]

Levetiracetam has good efficacy and an excellent safety profile. Most animal studies have revealed that levetiracetam does not cause neuronal apoptosis or disruption of synaptic development; in fact, it may have neuroprotective effects.[23–29] These qualities and the availability of an intravenous (IV) preparation have led to its widespread use in neonates, ahead of prospective evidence of its efficacy.[30,31] Because the neonatal response to anticonvulsants is fundamentally different from that of the older brain, specific study of levetiracetam within the neonatal population is essential; drugs that are effective in terminating seizures in older patients may be less effective and more toxic in neonates. The pharmacokinetics of levetiracetam in neonates have been studied.[32–34] The efficacy of levetiracetam used mostly as a second-line agent for neonatal seizures has been reported in case series to be between 30% and 84%.[35,36] NEOLEV2 was conducted with the specific objectives of studying the efficacy of levetiracetam compared with phenobarbital in the first-line treatment of neonatal seizures, the additional efficacy of loading-dose escalation from 40 to 60 mg/kg of levetiracetam, and the safety of levetiracetam in neonates.

METHODS

Study Design

NEOLEV2 was a multicenter, randomized, blinded, controlled, phase IIb efficacy, dose-escalation, and safety study of levetiracetam compared with phenobarbital in the first-line treatment of neonatal seizures. NEOLEV2 was an investigator-initiated, US Food and Drug Administration (FDA)-funded study. The participating hospitals were Rady Children's Hospital–San Diego; Sharp Mary Birch Hospital for Women & Newborns (San Diego, CA); University of California, San Diego Medical Center; University of California, San Francisco Benioff Children's Hospital (Oakland, CA); Auckland City Hospital (Auckland, New Zealand); and Loma Linda University Medical Center (Loma Linda, CA). The Loma Linda site closed early because of low recruitment. The study was approved by the institutional review boards of each center, and written consent was obtained from parents of all patients. A steering committee and separate data-safety monitoring board guided and monitored the study.

Inclusion and Exclusion Criteria

Infants at risk for developing seizures or suspected of having seizures were enrolled. Patients were term infants of a corrected gestational age between 36 and 44 weeks (<2 weeks of age) with a weight of at least 2.2 kg. Weight criteria were used to ensure that blood volumes drawn for monitoring were safe. Patients were excluded if they had received any previous anticonvulsants (with the exception of short-acting benzodiazepines administered for sedation >24 hours before enrollment), if the serum creatinine level was >1.6 mg/dL, or if seizures were due to correctable metabolic abnormalities (such as hypoglycemia or hypocalcemia). Patients in whom death was imminent were excluded. Patients in whom EEG monitoring could not be commenced before the need to treat definite clinical seizures were not recruited.

Eligible enrolled infants were started on continuous video EEG monitoring (cEEG). Seizures were defined as abrupt onset of rhythmic EEG activity lasting at least 10 seconds with a change in at least 2 of the following features: amplitude, frequency, or spatial distribution. Only neonates with electrographically confirmed seizures were treated. Video review was used to identify rhythmic artifact, such as patting or sucking.

Patients were randomly assigned to the levetiracetam or control phenobarbital treatment group in a 60:40 allocation ratio by using a block randomization strategy and stratified by site. Randomization lists, generated by the independent study statistical team, were communicated directly from the statistical center to the individual research pharmacies. Sterile dilution of phenobarbital injection (Westward or Martindale brand) was performed by research pharmacies, and prediluted Mylan-brand levetiracetam injection (15 mg/mL) was used according to a single standardized study protocol. Blinded study drugs were provided to the NICUs. All study investigators, medical staff, neurophysiologists, and patient families were blinded to treatment arm. Blinding was maintained by dilution of levetiracetam and phenobarbital such that the same volume (milliliters per kilogram) load was given to both treatment groups.

Our previous pharmacokinetic study of neonatal levetiracetam informed the loading and maintenance dosage of levetiracetam.[32] In adults on levetiracetam, trough concentrations are typically in the range 6 to 20 µg/mL. Given the intractability of neonatal seizures, for the dosing regimen, we aimed to maintain trough levels at >20 µg/mL for the first 3 days of treatment, when seizures are most active.[37,38]

Treatment Protocol

Patients confirmed to have electrographic seizures received infusion over 15 minutes of either levetiracetam at 40 mg/kg or the control treatment with phenobarbital at 20 mg/kg, with an additional 15 minutes allowed for the medication to take effect (Fig 1). If electrographic seizures persisted or recurred 15 minutes after the first infusion was complete, an additional dose of the same treatment type was given. Patients who had received levetiracetam at 40 mg/kg received an additional 20 mg/kg infusion over 15 minutes; patients who had received phenobarbital at 20 mg/kg received an additional 20 mg/kg infusion over 15 minutes. If electrographic seizures persisted or recurred 15 minutes after the second infusion was complete, the patient was then treated with the alternate treatment. The protocol ensured that the initial 40 mg/kg load of levetiracetam was completed a minimum of 45 minutes before the escalation to phenobarbital and balanced the need to ensure that all patients received standard-of-care treatment with phenobarbital within 60 minutes if levetiracetam was ineffective. Patients given any levetiracetam loading doses received maintenance levetiracetam at 10 mg/kg per dose, given IV every 8 hours for 5 days. Patients given any phenobarbital loading doses received maintenance phenobarbital at 1.5 mg/kg per dose, given IV every 8 hours for 5 days. The phenobarbital dose was divided this way to maintain blinding. If seizures persisted after treatment with both study drugs, patients exited the study protocol and received additional treatment according to institutional protocols.

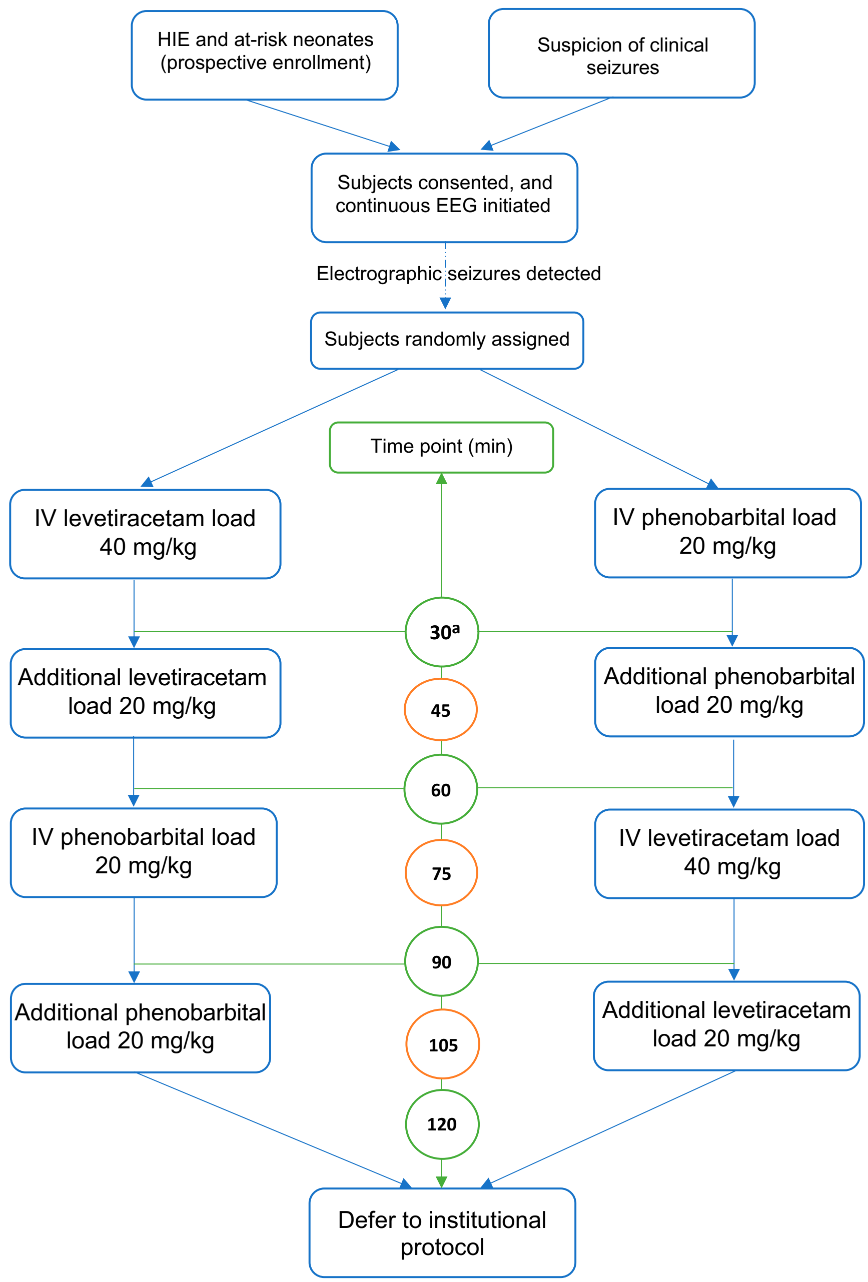

FIGURE 1
Study protocol and timing. [a]Progression to the next treatment occurs if electrographic seizures persist 15 minutes after completion of 15-minute infusion or recur within 24 hours.

EEG Monitoring and Assessment of Seizure Cessation

We developed an infrastructure for cEEG monitoring using remote review via the Internet, EEG technicians from a commercial EEG monitoring company (CortiCare) who continuously reviewed the EEG for the first 24 hours, and automated neonatal seizure detection software (Persyst, Solana Beach, CA) to optimize early seizure detection.[39] Cadwell EEG machines displaying 16-channel EEG and amplitude-integrated EEG were used. Neonates underwent cEEG monitoring for periods of 2 to 6 days. Neurologists at each site directed all anticonvulsant treatments.

Assessments of medication efficacy in seizure cessation were verified by review of the EEG by 2 independent neurophysiologists (S.L.D., J.J.G., S.W., M.N., N.R., M.L., or R.K.). Timed seizure markings from neurophysiologists were imported into a database. A third independent neurophysiologist (A.M. or S.L.D.) acted as a tiebreaker if discrepancies between the first 2 EEG reviewers impacted assessment of outcomes. Adjudication was required in 22 cases.

Outcomes

Seizure-Cessation Efficacy End Points

The primary outcome measure, which was validated by neurophysiologist review of the EEG, was the rate of achieving and maintaining electrographic seizure freedom for 24 hours. The original primary end point was 48-hour seizure freedom. After recruitment was complete, because EEG data were curated for data extraction, it was evident that EEG monitoring had been discontinued before 48 hours in many patients for clinical reasons, for example, to allow MRI or transfer of patients. After FDA approval, the primary outcome measure was, therefore, changed to 24-hour seizure cessation, which was the same time period used by Painter et al.[13] The statistical analysis plan was reviewed by the FDA and finalized before database lock and unblinding to ensure that no bias was introduced by this change. Seizure cessation for 48 hours was maintained as a secondary outcome. Other prespecified secondary outcomes included the rate of achieving and maintaining seizure freedom for 1 hour and subanalyses of the primary outcome measure for subjects with hypoxic-ischemic encephalopathy (HIE) who underwent therapeutic hypothermia.

Dose-Escalation Analysis

The percentage of subjects who achieved the primary outcome measure of seizure freedom for 24 hours after treatment with 60 mg/kg of levetiracetam (having not responded to 40 mg/kg of levetiracetam) was calculated.

Safety

Patient characteristics, drug dosing, safety laboratory tests, and adverse events were recorded by clinical trial coordinators at each site and entered into the study Research Electronic Data Capture[40] database hosted at University of California, San Diego. Because the study was conducted in a sick neonatal population, high rates of morbidity, clinical adverse events, abnormal laboratory values, and mortality were expected. In addition to the notification of recognized adverse events, systematic daily monitoring was conducted for hypotension, heart rate abnormality, respiratory abnormality, sedation, irritability, poor feeding, infection, need for oxygen, ventilation, or vasopressor treatment. A complete blood cell count and a comprehensive metabolic panel were measured before treatment and after 48 hours of treatment.

Statistical Analysis

Power calculations were based on a 2-sided χ^2 test for detecting a difference between 2 proportions, assuming a type 1 error of 0.05. With a sample size of 60 subjects receiving levetiracetam and 40 subjects receiving phenobarbital and assuming a seizure-cessation rate of 50% in the control arm,[13] the study had 80% power to detect an absolute difference in seizure outcome rates of ≥28% in the levetiracetam group.

Demographic and baseline characteristics of the 2 treatment groups were compared by using Fisher's exact test for categorical variables and the Wilcoxon rank test for continuous variables.

All efficacy outcomes were analyzed according to the randomized treatment assignment in a modified intention-to-treat population that included all randomly assigned subjects with neurophysiologist-confirmed seizures and a seizure-termination assessment at 24 hours. The primary outcome, which was a comparison of the 24-hour seizure-termination rate between the 2 treatment arms, was calculated by using Fisher's exact test. Secondary outcomes of 1- and 48-hour seizure-termination rates were analyzed similarly. A multivariate logistic regression analysis, adjusting for hypothermia treatment and HIE etiology, was performed as a secondary analysis. Three post hoc analyses were performed: to assess the possible impact of missing outcome data on the study results, post hoc sensitivity analyses using the best-worst case and worst-best case scores to impute missing primary outcome data were performed; an assessment of the primary outcome as assessed by the neurologist at the bedside was performed; and an additional post hoc analysis using a covariate-adjusted model, adjusted for baseline seizure severity, hypothermia treatment, and HIE etiology, was conducted.

Safety analyses were conducted on all randomly assigned participants. Fisher's exact tests were used to compare rates of adverse events, serious adverse events, study discontinuations, and deaths. All safety measures were analyzed by randomization arm (levetiracetam or phenobarbital) and by drugs received (levetiracetam, phenobarbital, or levetiracetam and phenobarbital). All analyses were repeated in the per-protocol population as well as in prespecified subgroups: hypothermia treatment and HIE etiology. There was no prespecified plan for adjustment for multiple comparisons of safety variables or secondary efficacy outcomes. However, all results are reported as point estimates and corresponding 95% confidence intervals (CIs) to provide an estimate of the variability of the estimate. Analyses were conducted by using the statistical software R (version 3.4.2; http://www.r-project.org).

RESULTS

Patient Enrollment, Study Completion, and Analysis

Between March 21, 2013, and October 31, 2017, 280 subjects consented to the study and underwent cEEG monitoring (Fig 2). One hundred six subjects were treated with study drugs for seizures. Five patients left the study before achieving the study end point. Thirty-five patients exited the study after the study end point but before completing 5 days of maintenance treatment. Twelve patients were excluded from the modified intention-to-treat population because neurophysiologists reviewing the EEG did not confirm the presence of seizures. In 11 patients, the primary outcome measure could not be obtained; in 5 of the 11, EEG data were either completely lost or missing at critical times; in 6 of the 11, efficacy data became uninterpretable (for details, see Fig 2). Two patients were excluded from the per-protocol population analysis because of protocol deviations. Eighty-three patients are included in the efficacy analysis (modified intention-to-treat population). There are 81 patients in the per-protocol analysis. Safety data were analyzed for all 106 treated patients.

Overall, 57 of 106 patients had HIE as the underlying cause of their seizures (54%); 42 patients underwent therapeutic hypothermia. Other seizure etiologies included stroke (18), hemorrhage (17), infection (6), brain malformation (5), pyridoxine-responsive epilepsy (2), drug withdrawal (2), glucose transporter defect (1), *KCNQ2* (2), and unknown cause (12). The groups were well balanced at baseline on demographics, clinical variables, and pretreatment seizure severity (Table 1). Ethnicity, race, pregnancy abnormality, delivery situation, mode of delivery, and anesthesia (not shown) were all distributed evenly between randomization arms.

Seizure Cessation Efficacy

Phenobarbital was more effective than levetiracetam in eradicating all seizures for 24 hours (primary outcome measure) (Tables 2 and 3, Fig 3). Of the patients randomly assigned to phenobarbital, 80% (24 of 30) remained seizure free for 24 hours, compared with 28% (15 of 53) of patients randomly assigned to levetiracetam ($P < .001$). Most patients randomly assigned to phenobarbital (70%; 21 of 30)

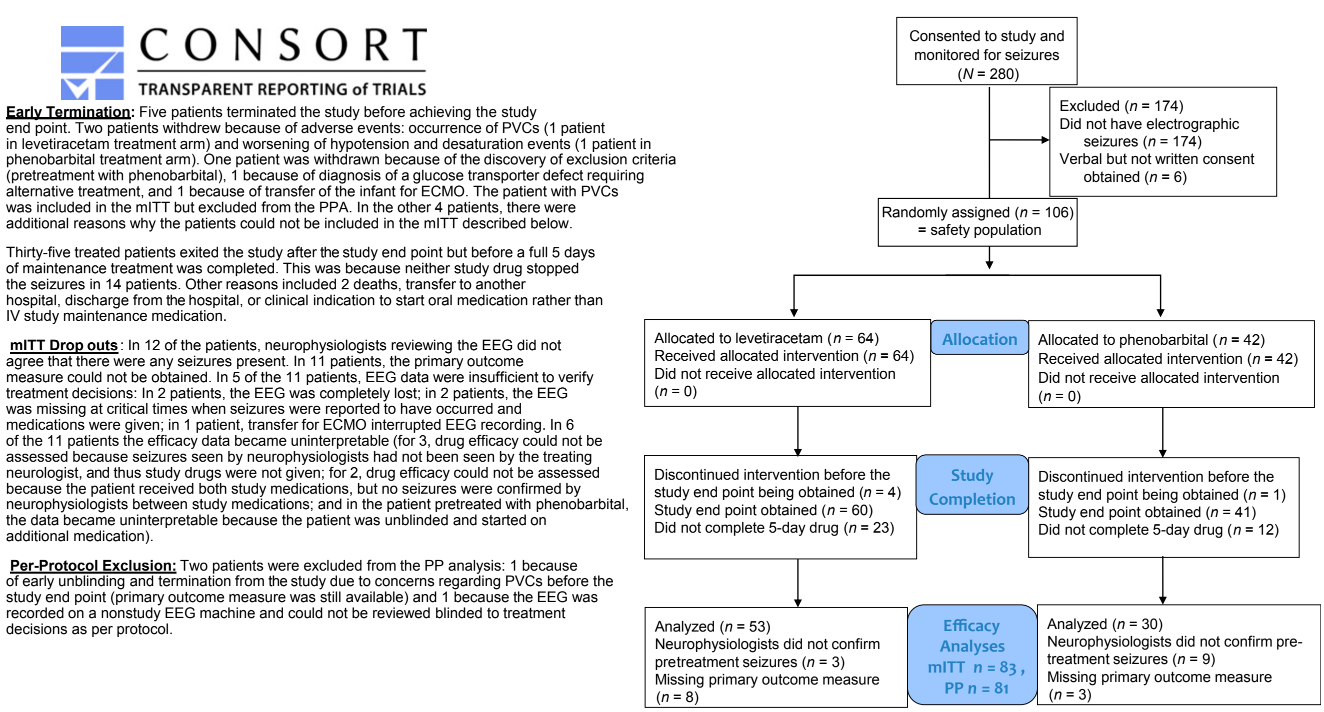

FIGURE 2

Consolidated Standards of Reporting Trials (CONSORT) flow diagram. ECMO, extracorporeal membrane oxygenation; mITT, modified intention-to-treat; PVC, premature ventricular contraction; PP, per protocol; PPA, per protocol analysis.

TABLE 1 Baseline Characteristics Compared Between Treatment Arms (All Randomly Assigned Participants)

	Levetiracetam	Phenobarbital	Overall	P[a]
HIE as seizure etiology, *n* (%)	35 (55)	22 (52)	57 (54)	Not tested
Received hypothermia treatment, *n* (%)	24 (38)	18 (43)	42 (40)	.7
Male sex, *n* (%)	31 (48)	24 (57)	55 (52)	.4
Cord pH				.2
n	31	20	51	—
Mean (SD)	7.07 (0.2)	7.15 (0.17)	7.1 (0.19)	—
Minimum, Q1, median	6.65, 6.94, 7.09	6.76, 6.99, 7.22	6.65, 6.99, 7.15	—
Q3, maximum	7.23, 7.35	7.28, 7.37	7.28, 7.37	—
5-min Apgar score				—
n	64	40	104	—
Mean (SD)	6.52 (3.01)	6.47 (2.4)	6.5 (2.78)	.6
Minimum, Q1, median, Q3, maximum	0, 4, 7.5, 9, 10	2, 4, 7, 9, 10	0, 4, 7, 9, 10	—
Gestational age				—
n	64	42	106	—
Mean (SD), wk	39.3 (1.3)	39.1 (1.3)	39.3 (1.3)	.3
Minimum, Q1, median, wk	36.4, 38.3, 39.5	36, 38.3, 39.3	36, 38.3, 39.4	—
Q3, maximum, wk	40.3, 41.6	40, 42	40, 42	—
Birth wt				
n	64	42	106	—
Mean (SD), g	3342 (577)	3317 (501)	3332 (546)	.9
Minimum, Q1, median, g	2070, 3051, 3303	2200, 2993, 3298	2070, 3033, 3298	—
Q3, maximum, g	3640, 4880	3745, 4300	3685, 4880	—
Pretreatment seizure severity				—
n	52	29	81	—
Mean (SD), min/h	12.3 (12.0)	9.1 (9.3)	11.1 (11.2)	.5
Minimum, Q1, median, Q3, maximum, min/h	0.5, 2.2, 7.1, 16.3, 41.2	0.2, 2.4, 6.8, 12, 38	0.2, 2.4, 7.0, 15.3, 41.2	—

Q1, lower quartile; Q3, upper quartile; —, not applicable.

[a] Fisher's exact test for categorical variables; Wilcoxon rank test for continuous variables.

remained seizure free with just a 20 mg/kg loading dose and maintenance. Covariate-adjusted analyses revealed results consistent with the results from the primary analysis (all $P < .001$).

Similar efficacy results were seen in the per-protocol population. Sensitivity analyses in which the missing outcome data were imputed were also consistent with the results from the primary analysis (Table 3). Patients with and without the primary outcome measure had similar baseline demographic characteristics.

Ninety-three percent of patients randomly assigned to phenobarbital were seizure free for at least 1 hour, compared with 49% of patients randomly assigned to levetiracetam. Sixty-four percent of patients randomly assigned to phenobarbital remained seizure free for 48 hours, compared with 17% of patients randomly assigned to levetiracetam. Similar efficacy results were seen in the subset of patients treated with hypothermia for HIE.

Dose-Escalation Data

Of the 42 patients who had ongoing seizures after 40 mg/kg of levetiracetam, the 20 mg/kg levetiracetam dose increment to 60 mg/kg resulted in seizure control for 24 hours in an additional 4 patients (7.5% increased efficacy of levetiracetam at 24 hours).

TABLE 2 Prespecified Primary and Secondary Outcome Measures (Modified Intention-To-Treat Population)

	Phenobarbital (20–40 mg/kg), *n* (Cessation %)	Levetiracetam (40–60 mg/kg), *n* (Cessation %)	Fisher's Exact P	Relative Risk (95% CI)
Primary outcome measure				
24-h seizure cessation rate (N = 83)	24 of 30 (80)	15 of 53 (28)	<0.001	0.35 (0.22–0.56)
Secondary outcome measures				
48-h Seizure cessation rate (N = 75)	18 of 28 (64)	8 of 47 (17)	<0.001	0.26 (0.13–0.53)
1-h Seizure cessation rate (N = 83)	28 of 30 (93)	26 of 53 (49)	<0.001	0.53 (0.39–0.7)
Subanalysis of patients with HIE treated with hypothermia				
24-h seizure cessation rate (N = 27)	9 of 10 (90)	6 of 17 (35)	0.014	0.39 (0.2–0.77)

TABLE 3 Post Hoc Analyses

	Phenobarbital (20–40 mg/kg), *n* (Cessation %)	Levetiracetam (40–60 mg/kg), *n* (Cessation %)	Fisher's Exact *P*	Relative Risk (95% CI)
Post hoc analysis: efficacy as assessed by a neurologist at the bedside				
24-h seizure cessation rate (N = 106)	35 of 42 (83)	23 of 64 (36)	<0.001	0.43 (0.3–0.61)
24-h seizure cessation rate (N = 94), excludes subjects without confirmed seizures	27 of 33 (82)	20 of 61 (33)	<0.001	0.4 (0.27–0.59)
Post hoc imputation analyses for missing primary outcome data				
Best-worst[a] case 24-h seizure cessation rate (N = 106)	36 of 42 (86)	18 of 64 (28)	<0.001	0.33 (0.22–0.49)
Worst-best[b] case 24-h seizure cessation rate (N = 106)	33 of 42 (79)	26 of 64 (41)	<0.001	0.52 (0.37–0.72)

[a] In the analysis, no patients randomly assigned to levetiracetam with a missing primary outcome measure were imputed as seizure free to 24 h, and all patients randomly assigned to phenobarbital with a missing primary outcome measure were imputed as seizure free to 24 h. Patients in whom seizures were not confirmed were imputed as seizure free to 24 h.
[b] In the analysis all patients randomly assigned to levetiracetam with a missing primary outcome measure were imputed as seizure free to 24 h, and no patients randomly assigned to phenobarbital with a missing primary outcome measure were imputed as seizure free to 24 h. Patients in whom seizures were not confirmed were imputed as seizure free at 24 h.

Safety Analyses

Three patients died during the study period, and 3 patients died after the study period but within the neonatal period (Table 4). One patient died of subgaleal hemorrhage and HIE, and 5 were withdrawn from life support because of severe HIE. By using standardized definitions for the grading of adverse events,[41] additional grade 4 serious adverse events affected an additional 6 patients: 5 patients experienced hypotension, and 1 patient experienced respiratory depression that was probably or possibly due to the study medication. Milder adverse events were recorded on at least 1 study day in 25 patients. Adverse events, including hypotension, respiratory suppression, sedation, and requirement for pressor support, were more common in patients randomly assigned to phenobarbital. Patients who received only 20 mg/kg of phenobarbital still experienced higher rates of adverse events (column 7 in Table 4). As would be expected in a phase IIb study, powered for the primary outcome analysis, these differences were not statistically significant.

Laboratory Data

In 80 of 106 patients, the full set of monitoring laboratory data, collected after 48 hours on treatment with the study drug, was available. No significant treatment-emergent trends were seen for either treatment arm in these data (Supplemental Information).

DISCUSSION

NEOLEV2 provides randomized controlled prospective efficacy data for levetiracetam and phenobarbital in neonates in the hypothermia era. Previous data come from uncontrolled case series, often retrospective, using levetiracetam for second-line treatment, and without cEEG assessment or neurophysiologist review.[35,36,42,43] Given the high rates of subclinical seizures and abnormal movements without electrographic seizures seen in neonates, cEEG monitoring is vital to validate any neonatal seizure research. The waxing-then-waning time course of acute symptomatic seizures particularly makes data from uncontrolled studies and second-line treatment studies unreliable.[37,38,44] It is recognized that timeliness in the treatment of seizures can double the efficacy of anticonvulsants.[45] Systematic cEEG monitoring, remote review, and seizure detection technologies optimized early identification of seizures in NEOLEV2 and may have improved drug efficacy.[39] To our knowledge, in no other pediatric treatment trial have investigators attempted real-time response to cEEG-detected seizures. An additional strength of the study is the validation of seizure diagnosis and drug-efficacy assessments by 2 independent neurophysiologists. Because we recruited all comers with seizures, our results are generalizable to all term neonates with seizures. The subanalysis of patients with acute symptomatic seizures due to HIE suggests our results are generalizable to that important group.

We observed greater efficacy of phenobarbital than that reported by Painter et al,[13] in which patients received on average 35 mg/kg of phenobarbital titrated to serum levels. In that study, the authors recruited patients with more severe seizures, and the study was conducted before hypothermia, which reduces neonatal seizures and increases treatment response,[37,46] becoming the standard of care for HIE. Our data reveal clinically important, albeit not statistically significant, differences in the side-effect profile of levetiracetam compared with phenobarbital. Increased rates of sedation, respiratory suppression, and hypotension were demonstrated with phenobarbital, including in patients who received 20 mg/kg. It is unclear why Painter et al[13] found no adverse side effects. Hypothermia and morphine cotreatment may exacerbate the side effects of phenobarbital.

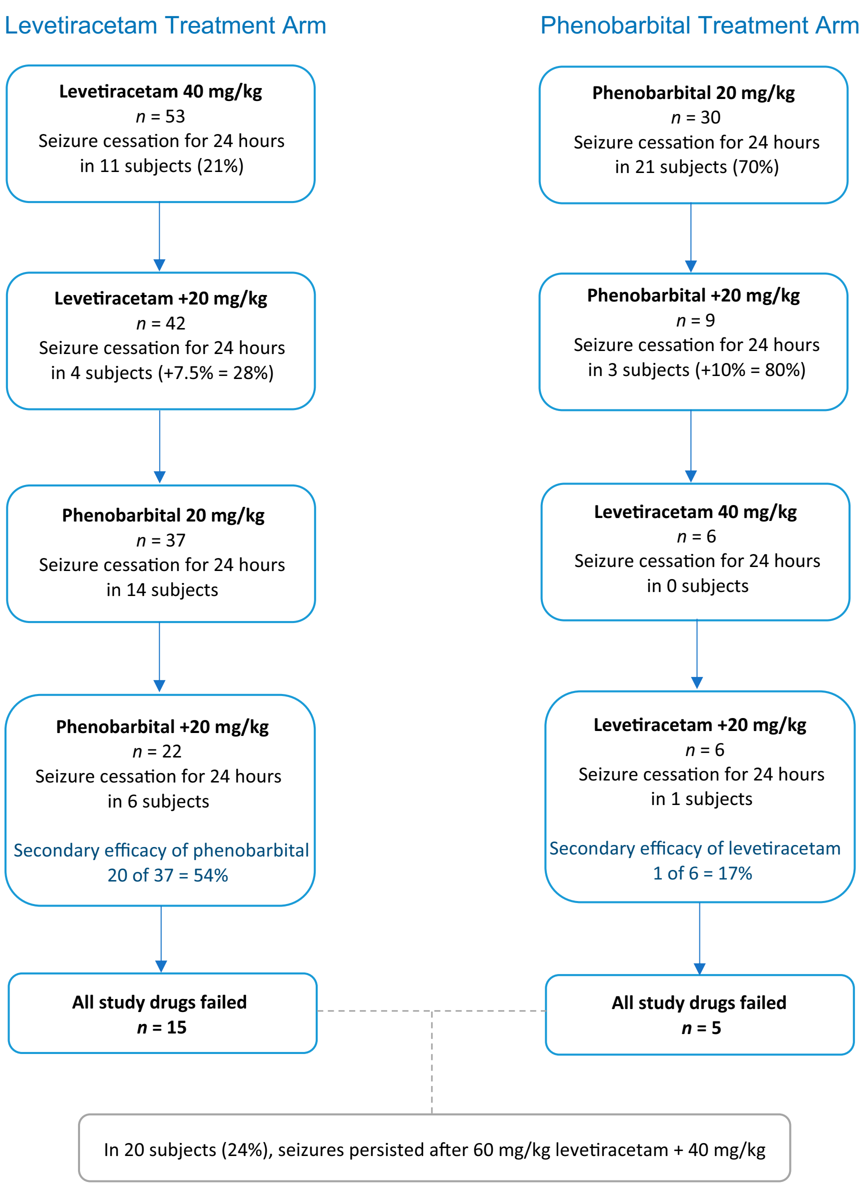

FIGURE 3
Results: Treatment response flowchart.

Sixty milligrams per kilogram is the maximal dose for which levetiracetam is licensed in any age group, and therefore it is as high as was ethical in this first controlled study in vulnerable neonates. Case series in children have revealed that high doses of levetiracetam (up to 275 mg/kg per day) can achieve seizure freedom when standard dosing has failed.[47,48] If higher-dose levetiracetam has increased efficacy in neonatal seizures, the excellent safety profile of levetiracetam should be exploited to realize this potential. The increased efficacy seen with modest dose escalation in NEOLEV2 is encouraging in this regard.

The exclusion of 23 patients from the modified intention-to-treat population is a limitation of our study. This resulted from our stipulation that seizure diagnosis and cessation must be validated by neurophysiologist review, which is a necessary rigor given interrater variability in neonatal cEEG interpretation.[49–51] Using assessments by the neurologist at the bedside for the primary outcome would have been less accurate. Because of the consistency of results observed from best-worst case sensitivity analyses and analysis by using the assessment by the neurologist at the bedside, we are confident that the missing outcome data did not significantly bias our results (Table 3).

We began treatment whenever a seizure was confirmed, and some patients with low pretreatment seizure burden may have had resolution of their seizures without any drug treatment. A higher seizure burden pretreatment of at least 30 seconds/hour is recommended in new guidelines and would have avoided drug treatment in some patients and improved interreader agreement for electrographic seizure diagnosis.[44]

The chief limitation of this study is its short-term end point. For our aim of obtaining preliminary prospective efficacy data for levetiracetam in neonates, it was appropriate to use seizure cessation as the primary outcome measure. However, the end point of greatest concern in neonatal seizure trials is long-term neurodevelopmental outcome. A drug that is less effective in achieving seizure cessation but leads to a better neurodevelopmental outcome through a neuroprotective effect or lack of neurotoxicity may be the preferred first-line treatment option. Once optimal dosing is defined for levetiracetam and other candidate treatments for neonatal seizures, much larger neonatal seizure trials will be needed to study these long-term outcomes and guide treatment decisions definitively.

CONCLUSIONS

This phase IIb study has revealed greater efficacy of 20 to 40 mg/kg of

TABLE 4 Deaths, SAEs, and Other Adverse Events (All Randomly Assigned Participants)

	Randomized Treatment Arm					Drugs Received			
	Phenobarbital (N = 42), n (%)	Levetiracetam (N = 64), n (%)	All (N = 106), n (%)	Fisher's Exact Test, P	Relative Risk (95% CI)	Phenobarbital Only (N = 32), n (%)	Phenobarbital, 20 mg/kg Only (N = 22), n (%)	Levetiracetam Only (N = 19), n (%)	Levetiracetam and Phenobarbital (N = 55), n (%)
Death during study	1 (2)	2 (3)	3 (3)	—	—	0 (0)	0 (0)	0 (0)	3 (5)
Neonatal death after study	0 (0)	3 (5)	3 (3)	—	—	0 (0)	0 (0)	0 (0)	3 (5)
Grade 4 or 5 AE or SAE	5 (12)	4 (6)	9 (8)	.48	0.52 (0.15–1.84)	3 (9)	2 (9)	1 (5)	5 (9)
AE on at least 1 d	13 (31)	12 (19)	25 (24)	.17	0.61 (0.31–1.2)	9 (28)	7 (32)	3 (16)	13 (24)
Hypotension AE[a]	7 (17)	3 (5)	10 (9)	.05	0.28 (0.08–1.03)	5 (16)	4 (18)	0 (0)	5 (9)
Respiratory abnormality AE[a]	11 (26)	8 (13)	19 (18)	.12	0.48 (0.21–1.09)	8 (25)	6 (27)	1 (5)	10 (18)
Sedation AE[a]	8 (19)	7 (11)	15 (14)	.27	0.57 (0.23–1.47)	5 (16)	4 (18)	1 (5)	9 (16)
Heart rate abnormality AE[a]	1 (2)	3 (5)	4 (4)	>.99	1.97 (0.21–18.3)	1 (3)	1 (5)	1 (5)	2 (4)
Poor feeding AE[a]	7 (17)	6 (9)	13 (12)	.36	0.56 (0.2–1.56)	5 (16)	4 (18)	1 (5)	7 (13)
Infection AE[a]	3 (7)	2 (3)	5 (5)	.38	0.44 (0.08–2.51)	3 (9.4)	2 (9)	1 (5)	1 (2)
Vasopressor support[b]	13 (31)	10 (16)	23 (22)	.09	0.5 (0.24–1.04)	12 (22)	7 (32)	1 (5)	10 (31)
Ventilated[b]	19 (45)	24 (38)	43 (41)	.54	0.83 (0.52–1.31)	10 (31)	8 (36)	4 (21)	27 (49)
Oxygen required[b]	24 (57)	38 (59)	62 (59)	.84	1.04 (0.75–1.45)	17 (53)	12 (55)	9 (47)	36 (66)

AE, adverse event; SAE, serious adverse event; —, not applicable.

[a] Patients in whom this clinical problem and an AE was documented on the same day.

[b] Patients in whom this support was required on at least 1 d.

phenobarbital than 40 to 60 mg/kg of levetiracetam. More adverse events occurred with phenobarbital. Higher-dose studies of levetiracetam are warranted, and definitive studies with long-term outcome measures are needed.

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ABBREVIATIONS

cEEG: continuous video EEG monitoring
CI: confidence interval
FDA: US Food and Drug Administration
HIE: hypoxic-ischemic encephalopathy
IV: intravenous(ly)

Dr Haas conceived and designed the study, provided overall supervision, recruited and studied subjects, interpreted the data, and critically revised the manuscript; Dr Sharpe conceived and designed the study, recruited and studied subjects, obtained data, provided supervision, interpreted data, and wrote the initial draft of the manuscript; Dr Reiner contributed to the study design, recruited and studied subjects, constructed and supervised the database, obtained data, and critically revised the manuscript; Ms Lee assisted with the construction and supervision of the database and contributed to and critically revised the manuscript; Ms Ernstrom and Dr Raman contributed to the design of the study, performed the statistical analyses, interpreted the data, and critically revised the manuscript; Ms Davis, Drs Nespeca, Gold, Wang, Rismanchi, Kuperman, Le, Mower, Rasmussen, Harbert, Michelson, Joe, and Kim, Mr Battin, Drs Lane and Honold, Ms Knodel, Ms Arnell, and Ms Bridge each made substantial contributions to the acquisition and analysis of data and critically revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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